

Mighty Mice

Dr. Richard Hanson has been studying metabolism¹ at Case Western Reserve University for over twenty years. In particular, he was studying the enzyme,² phosphoenolpyruvate carboxykinase³, or PEPCK, which is important in the production of glucose.⁴ The process is called gluconeogenesis⁵ and it takes place primarily in the liver⁶ and kidney cortex.⁷

Dr. Hanson decided to test the function of PEPCK by over-expressing⁸ the enzyme in skeletal muscle of mice. “This is a very common technique,” said Dr. Hanson. “There are three possible results: the animal will die, nothing will happen, or there will be some identifiable changes. We were expecting some subtle changes that would give us a clue as to the biological function of PEPCK in skeletal muscle.” Dr. Hanson never expected such astounding results: a mouse that could run for five kilometers!

¹ *Metabolism*: The collection of reactions in your body that convert food into energy.

http://www.kidshealth.org/parent/general/body_basics/metabolism.html

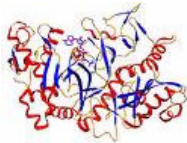
² *Enzyme*: Any protein that acts as a catalyst for a chemical reaction.

<http://www.medterms.com/script/main/art.asp?articlekey=3266>

³ *PEPCK*: The enzyme that catalyzes the reversible rate-controlling step of gluconeogenesis, the process that makes glucose. The majority of gluconeogenesis takes place in the liver. The reaction involves the decarboxylation of oxalacetate to phosphoenolpyruvate, with GHTP as an energy source.

http://en.wikipedia.org/wiki/Phosphoenolpyruvate_carboxykinase

<http://en.wikipedia.org/wiki/Gluconeogenesis>



⁴ *Glucose*: A simple sugar that is an important carbohydrate in biology. <http://en.wikipedia.org/wiki/Glucose>



⁵ *Gluconeogenesis*: The production of glucose from non-sugar carbon substrates like pyruvate, lactate, glycerol, and glucogenic amino acids. The majority of gluconeogenesis takes place in the liver.

<http://en.wikipedia.org/wiki/Gluconeogenesis>

⁶ *Liver*: Controls lipid, protein, and carbohydrate synthesis and bodily excretion.

<http://www.vivo.colostate.edu/hbooks/pathphys/digestion/liver/index.html>

⁷ *Kidney cortex*: The outer part of the kidney. <http://cancerweb.ncl.ac.uk/cgi-bin/omd?kidney+cortex>

⁸ *Over-expressing*: Producing a lot of a particular gene.

These mice are transgenic,⁹ which means they were created by inserting the gene for PEPCK, which contained a skeletal muscle-specific gene promoter, into the germline¹⁰ of a fertilized mouse egg. The transgenic mice grow to maturity and over-express the PEPCK gene in skeletal muscle.

Dr. Hanson's associate, Parvin Hakimi, immediately noticed a difference between the transgenic mice and control animals by their behavior in their home cage; they were constantly in motion. When the scientists tested the activity levels of the mice in the Case Western Reserve University School of Medicine Mouse Behavioral Core Lab, they found that the transgenic mice were ten times more active than controls. The differences did not stop there. The transgenic mice were half the size of the controls, and they ate almost twice as much. They also lived longer than their control counterparts. The female transgenic mice had an increased reproductive capacity¹¹ (one mouse recently gave birth to a normal litter of pups at 35 months of age) and the male transgenic mice were much more aggressive than normal.

The researchers also found profound biological¹² differences between the transgenic and control mice. The skeletal muscle of the mice had many more mitochondria,¹³ and they hardly produced any lactic acid during intense exercise. Lactic acid is a product of glucose breakdown, which is responsible for making your muscles sore after you exercise. In the presence of oxygen,

⁹ *Transgenic*: The process of transferring a gene or genes from one species to another.

http://en.wikipedia.org/wiki/Transgenic_plant

¹⁰ *Germline*: Cells (sperm and eggs) that have genetic material that may be passed to a child.

<http://en.wikipedia.org/wiki/Germline>

¹¹ *Reproductive capacity*: How many offspring an organism is able to produce.

¹² *Biological*: Pertaining to bodily functions as opposed to behavioral functions.

¹³ *Mitochondria*: The organelle where ATP is produced. <http://www.cellsalive.com/cells/mitochon.htm>

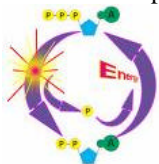


cells generate energy through ATP¹⁴ produced from cellular respiration.¹⁵ When you exercise, though, there may not be enough oxygen to fully support cellular respiration, so cells produce ATP via aerobic glycolysis.¹⁶ This process is not nearly as productive as respiration in the presence of oxygen, and one of its main byproducts is lactic acid. If the transgenic mice were not producing large amounts of lactic acid, it means they were getting their energy from somewhere else. In fact, they are oxidizing fatty acids derived from the triglycerides,¹⁷ stored in their skeletal muscle where the PEPCCK was over-expressed.

The primary advantage of these “super mice” is as a tool to understand how high levels of activity of PEPCCK can make these animals more energetic, live longer and reproduce longer. These results have left Hanson wondering about the biological function of PEPCCK. Why is there such a behavioral modification? Why do the mice get so aggressive? Why do they eat more? Why do they live longer? “We would really like to know that,” says Dr. Hanson.

Dr. Hanson began by trying to explain why the transgenic mice eat more food and reasoned that the hormones¹⁸ regulating appetite may be involved. There are two important

¹⁴ ATP: Transports chemical energy within cells. http://en.wikipedia.org/wiki/Adenosine_triphosphate

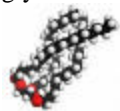


¹⁵ Cellular respiration: The process by which sugar, in the form of glucose, is made into energy.

http://www.phschool.com/science/biology_place/biocoach/cellresp/intro.html

¹⁶ Fermentation: The process of turning glucose into energy when oxygen is not present. Fermentation is used by organisms such as yeast and also in humans during exercise when there is not enough oxygen for cellular respiration.

¹⁷ Triglycerides: The main constituent of vegetable oil and animal fats, it consists of a glyceride in which the glycerol has three fatty acids. <http://en.wikipedia.org/wiki/Triglyceride>



¹⁸ Hormones: Chemicals that are secreted by one organ into the blood stream to function at a different location in the body. <http://www.nlm.nih.gov/medlineplus/hormones.html>

hormones that suppress appetite: insulin,¹⁹ which is released from the beta-cells of the pancreas,²⁰ and leptin,²¹ which is produced in adipose tissue.²² The transgenic mice have very little of both of these hormones, which would normally suppress appetite. This is most likely the reason why the mice eat more.

It does not, however, explain why these mice are in constant motion. Another hypothesis is that PEPCK is responsible for the production of the glycerol²³ backbone of the triglyceride fatty acids. Perhaps the transgenic animals are so active because the over-expressed PEPCK is making too many triglycerides in skeletal muscle that the mice then have to use.

The longevity of the mice raises questions about the current theories of aging. All of the literature on aging agrees that restricting the number of calories consumed increases lifespan. But these transgenic mice eat twice as much as the control animals and live longer. Maybe the answer to a longer life is not in your caloric intake, but in how you use those calories.²⁴ The transgenic mice ate much more than the controls, but they also hyperactive. Dr. Hanson believes the way to a longer life is through exercise, not simply through calorie reduction. “There are so many things we still want to know,” said Dr. Hanson, “this is just the beginning.”

¹⁹ *Insulin*: A hormone, secreted from the pancreas, that regulates blood sugar.
<http://www.endocrineweb.com/diabetes/2insulin.html>

²⁰ *Pancreas*: An organ found right below the stomach that is involved in metabolism.
<http://www.mamashealth.com/organs/pancreas.asp>



²¹ *Leptin*: A hormone that regulates body weight, metabolism, and reproductive function.
<http://www.vivo.colostate.edu/hbooks/pathphys/endocrine/bodyweight/leptin.html>

²² *Adipose tissue*: Loose connective tissue, commonly known as fat, that aids in storing energy.
http://www.sciencedaily.com/articles/a/adipose_tissue.htm

²³ *Glycerol*:

²⁴ *Calories*: A measurement of energy. <http://en.wikipedia.org/wiki/Calorie>

Dr. Richard Hanson is a Professor of Biochemistry²⁵ at Case Western Reserve University in Cleveland, Ohio who studies metabolism. He began his training as a biology²⁶ major at Northeastern University in Boston, Massachusetts. Dr. Hanson chose Northeastern because of the work-study program, and he spent his first time co-op working in a laboratory at nearby Tufts University. "When I went to graduate school," he said, "I was well trained already because I had laboratory experience gained at my co-operative work job." Dr. Hanson received his Ph.D. from Brown University. Dr. Hanson enjoys teaching medical students and says the most important thing he can do is to positively influence young people and help them with their future careers.

TO LEARN MORE:

1. Hanson, Richard, et al. "Overexpression of the Cytosolic Form of Phosphoenopyruvate Carboxykinase (GTP) in Skeletal Muscle Repatterns Energy Metabolism in the Mouse." *The Journal of Biological Chemistry* 282(2007): 32844-32855.

FOR MORE INFORMATION:

1. The National Institutes of Health <http://health.nih.gov/search.asp/29>

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²⁵ *Biochemistry*: The study of chemistry in biological processes. <http://dictionary.reference.com/browse/biochemistry>

²⁶ *Biology*: The study of living organisms and all their forms. <http://dictionary.reference.com/browse/biology>